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Invited Commentary

Barriers to Brain Stimulation Therapies for Treatment-Resistant Depression: Beyond Cost Effectiveness

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In this issue of the journal, Fitzgibbon and colleagues create an elaborate simulation model based on a broad consideration of costs and treatment efficacies to determine the comparative cost-effectiveness of rapid transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) in management of treatment-resistant depression (TRD).[1]

In so doing, they take the oldest continuing biological intervention in psychiatry, ECT—arguably our field's most effective and most stigmatized treatment—and stack it up against one of our newer forms of brain stimulation. Even though rTMS has been subject to more than two decades of multiple randomized controlled trials in depression as well as network meta-analyses,[2] it remains unknown or unfamiliar to many health professionals, patients, and families. While many generations of clinicians easily recall patients they knew who received and benefited from ECT, very few have a personal data bank of patients treated with rTMS. If ECT has secured a firm—if controversial—place in our therapeutic armamentarium and cultural history, rTMS is still virtually unavailable in most clinical settings and not yet a therapeutic skill that is a core part of psychiatry training.

Depression is the leading cause of disability globally. In Ontario, depression alone represented a greater burden of disease (as reflected by years lived with disability and years lost due to premature death) than lung, prostate, colon, and breast cancer combined.[3] Although we have reasonably effective psychological and pharmacological treatments for depression, too many people are left in a state of TRD after countless drug trials and drug combinations or extensive courses of psychotherapy. In the context of therapeutic frustration, it can even result in familiar patient-blaming verbal lapses such as, "the patient failed a trial of . . ." We need to own the reality that our treatments fail some patients, not the other way around. There is both a clinical and economic imperative to develop new options as well as to use existing evidence-based options.

ECT was developed over 80 years ago, spread rapidly around the globe, and remains for a number of psychiatrists the treatment they would want for themselves if they became severely depressed—a good yardstick to use when recommending treatments for other people.[4] Jeff Daskalakis, co-director of the Temerty Centre for Therapeutic Brain Intervention at the Centre for Addiction and Mental Health (arguably the busiest center in the country for both ECT and rTMS), often states that the numbers needed to treat for ECT in TRD is 2 to 3 (based on a 65% remission rate for ECT in TRD vs. a 15% remission rate for placebo)—an astonishingly low number that very few treatments throughout medicine could match.[5] However, it remains an intrusive and intensive treatment with significant cognitive sequelae, and the need for alternatives persists.

In considering alternative forms of brain stimulation to ECT, the concept of stepped care is crucial. Fitzgibbon and colleagues have presented a model and data to show the rTMS pathway was a more cost-effective first-line treatment than ECT for TRD—and that the best outcomes overall are when patients with TRD start with rTMS and then proceed to ECT only if rTMS didn't work. This is the essence of stepped-care thinking: Start with a treatment that is more benign, even if it may have lower narrowly defined positive clinical outcome rates, and follow this with more intrusive and disruptive and costly treatments only if clinically necessary. Since rTMS is easily administered on an outpatient basis, with no need for patient accompaniment home afterward, no need for anesthesia, no induction of a

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seizure, and no cognitive sequelae, it is more benign an intervention than ECT.

Indeed, the 2016 Canadian Network for Mood and Anxiety Treatments depression guidelines list rTMS as a first-line treatment for patients with depression where at least one antidepressant has failed them. However, these guidelines are also clear that the clinical effectiveness—as opposed to cost-effectiveness—of rTMS is less than that of ECT and that "rTMS should be considered prior to pursuing ECT and that patients who have not responded to ECT are unlikely to respond to rTMS."[6] In other words, stepping up from rTMS to ECT is a one-way staircase.

So what are the barriers to rTMS and ECT? The first barrier is access. Although a national survey of 175 ECT services across Canada, based on 2006 data, reported that 84% of the Canadian population lived within a 1-hr drive to an ECT center, geographic proximity is not the same as access.[7] The study points to numerous other pragmatic barriers, including lack of funding for modern equipment, lack of anesthesiology support, space limitations capping the numbers of people treated, and logistical challenges to delivering this treatment on an outpatient basis (which markedly reduces associated costs). This national survey also provided an important snapshot on utilization and treatment practices in 2006.[8] However, more recent administrative database research in Quebec covering 1996 to 2013 reveals a significant decrease in rates of acute ECT use for all age groups and both sexes, with less than 1% of people being treated for mental disorders receiving ECT.[9] According to a recent database study of over 47 million privately insured Americans, only 0.25% of those diagnosed with a major depressive episode or bipolar disorder received ECT in 2014, and that utilization rates are declining.[10]

At the Centre for Addiction and Mental Health, dedicated space for ECT treatment and recovery, as well as a specialized team of psychiatrists, nurses, and anesthesiologists, allows for the operation of a 5-day-per-week service that can efficiently treat 30 or more patients per morning, predominantly outpatients, with both acute and maintenance ECT. After an initial consultation by a psychiatrist specialized in brain stimulation and an anesthesiologist, there is essentially no delay in the initiation of acute treatment.

A second barrier is education of health professionals. National studies of the training of Canadian psychiatry residents in ECT historically have revealed marked inconsistency and inadequacy[11] and, in the 35-year experience of the first author D.S.G., consistent resident exposure to and training in the ongoing practice of ECT is the exception rather than the norm. This leads to barriers not only with regard to skills but also in knowledge and attitudes among practitioners. If the next generation of psychiatrists is not adequately trained to use appropriately the most effective treatment for the most severely ill and treatment-resistant depressed patients, how will they tailor their clinical practices and, more importantly, what will be the impact for patients?

The third barrier is stigma. Recent qualitative research among Danish recipients and health professionals reveals the breadth of stigma and self-stigma even among people who felt that ECT helped them, sometimes dramatically[12]; ECT recipients described devaluation and alienation by others as a consequence of people knowing they received ECT. Professional experts decried the portrayals (and implied purpose) of ECT in popular culture, and both groups perceived structural discrimination against ECT recipients.

If ECT is forever enshrined in the public imagination by films such as *One Flew Over the Cuckoo's Nest* or television shows like *Homeland*, rTMS remains unknown to the general public and unused by the majority of psychiatrists. There are no popular culture images of rTMS apart from an occasional television news feature, and most psychiatrists have likely never seen rTMS administered, with a patient sitting in a chair while a technician positions an induction coil against a targeted scalp area and delivers focused magnetic pulses, typically once per day for 20 to 30 sessions. But, like ECT, there are structural barriers—the costs of equipment, the need for space and technicians, and the appropriate public funding of physicians in overseeing the treatment. The evidence for effectiveness using 21st century standards of research has leapfrogged ahead of availability and training. The advantages of not requiring general anesthesia or an induced convulsion, as well as not generating memory loss, should kindle enthusiasm for this new and evidence-based intervention among patients, providers, and funders given the prevalence, cost, and pain of TRD. rTMS has been approved by Health Canada for treatment of depression since 2002. But national approval has not translated into national availability, and fewer than half of Canada's provinces and territories have funded public treatment. Saskatchewan has a physician fee code for rTMS, while Alberta and Quebec have made funding available to specific rTMS centers.[13] In the context of limited public investment, private-sector rTMS services have evolved as an option in multiple provinces.

The made-in-Canada effectiveness evidence for rTMS is available, and with Fitzgibbon et al.'s modeling paper, the cost-effectiveness evidence has also been generated. These should help break down the other barriers to implementation of and meaningful access to rTMS and ECT if we are truly committed to alleviating the mental suffering of an estimated 700,000 Canadians who experience TRD.

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